GENETIC SERVICES IN ARIZONA

4TH EDITION

Compiled by

Members of the Genetics
Advisory Committee of the
Arizona Department of Health Services

Edited by
Ann Bogle, PhD, CGC
Jane Congleton, MS, RN, CGC
Pamela J. Nutting, MS, CGC
Sarah Richter Cox, MS, CGC
Betsy Trombino

Forward to the Fourth Edition

With the scientific advances in knowledge brought about by the Human Genome Project (HGP), health professionals and consumers will need to be more educated about genetics, genetic testing, and the options available. The HGP will identify the function of all the genes in the genome, including those involved with disease. More alternatives will be available for diagnostic testing as well as better and more effective, targeted treatment.

Almost daily, the news media reports advances in genetics. Specific genes are being identified which may be associated with protection from a disease or development of diseases or chronic conditions. For example, there is a gene that confers protection against HIV infection and the development of AIDS. Another gene for heredity hemochromatosis leads to significant morbidity and mortality from iron overload. This disorder is under diagnosed and thus many individuals go untreated. Genes, like BRCA 1 and others, are associated with an increased risk of breast and ovarian cancer. There is an urgent need to educate health professionals, so they can be better informed about the potential benefits, risks, and limitations of genetic tests.

A new era in pharmacogenetics is evolving. In the not too distant future, gene testing will occur before decisions are made as to what drugs would be most effective and least toxic for a specific individual.

More information is needed by many health professionals to assist people in their decision making about whether or not to have a genetic test. Information is also needed about when and whom to refer for genetic counseling.

As genetic professionals, we are committed to educating not only our patients, but health care providers and consumers. This is a very large agenda in the state of Arizona for such a small number of genetics professionals. This booklet is one attempt to continue this educational process.

Jane Congleton, MS, RN, CGC

Table of Contents

SECTION I. THE MEANING AND PURPOSE OF GENETIC SERVICES

Genetic Diagnosis, Management, and Counseling

This chapter will review the importance of providing a specific diagnosis, ways that medical management may alter the character or course of a genetic disorder, the process of genetic counseling, and a list of locations in Arizona where genetic services are provided.

The Importance of Diagnosis of Genetic Disorders

Perhaps the most important distinguishing characteristic of genetic disorders is their tendency to recur. Unlike infectious diseases, which may occur in anyone who makes the necessary type of contact with an affected person, genetic disorders recur in a few distinct patterns to people with specific relationships to the affected individuals. Once a specific genetic disorder has been identified, it may be possible to define the pattern of inheritance. This will determine who in a family or genetic population is at risk, as well as their degrees of risk, as shown in Table 1.

Genetic or etiologic heterogeneity is a term used to describe the finding that the same or very similar clinical manifestations can result from different genetic or non-genetic conditions. A striking example of this phenomenon is the visible similarity between individuals with Turner syndrome and Noonan syndrome. Turner syndrome is caused by the absence of one of the sex chromosomes in females. Those individuals born with Noonan syndrome have a disorder resulting from an abnormality of a single gene. In the former case, the chance that a sibling or child of the affected individual will be born with Turner syndrome is negligible (in fact, infertility is the rule for women with this condition). Whereas in the latter case, the chance that a sibling or child of the affected individual will be born with Noonan syndrome may be as high as 50%. These two disorders also have different associated medical and intellectual problems, and require different kinds of medical evaluation, treatment, and community services.

Thus, making a specific diagnosis in genetic disorders is extremely important for predicting the course of the condition in the affected individual, identifying additional family members at risk for the condition, and/or determining the risk of having affected children. Options for altering the risks of recurrence, based upon family planning and prenatal diagnosis, can then be offered to the at-risk individuals.

Management Issues in Genetic Disorders

Because many genetic disorders are constitutional, many people believe they are not amenable to treatment by conventional medical therapies. This is far from the truth. Medical management of many of these conditions can result in dramatic improvement in outcome. This is most easily demonstrated for metabolic disorders where alteration of the diet or replacement of a missing enzyme can, in essence, prevent all or almost all serious health and developmental effects of the disorder. Because many of the metabolic disorders are treatable, some have been chosen for testing in the current national system of newborn metabolic screening tests. This allows determination of affected individuals in the newborn period and initiation of treatments that prevent the adverse consequences of the disorder. The classic example of this phenomenon is the identification and management of newborns with phenylketonuria (PKU), a deficiency of the enzyme phenylalanine hydroxylase which converts phenylalanine to tyrosine. In PKU, blockage of this enzyme leads to a build up of phenylalanine which is toxic to the developing brain. Untreated individuals have severe mental retardation, seizures, and life long neurological impairment. However, if phenylalanine is restricted in the diet of a newborn, and the individual consistently follows this special diet, then development and intellectual functioning are normal. Many other metabolic disorders can be tested for and managed in a similar fashion. Another type of secondary prevention for genetic conditions involves the anticipation (early detection) of the silent manifestations of genetic disorders. For example, in the condition known as hemochromatosis, the person who is homozygous for this disorder will usually develop cirrhosis, diabetes, and heart failure from excessive iron stores, if left untreated. However, early diagnosis of this common disorder can prevent iron build-up and through medical management leads to avoidance of these consequences. Another example is neurofibromatosis, for which annual preventative physical examinations can detect early (and treatable) manifesta-tions, such as tumors, hypertension, or scoliosis.

This type of medical management can alter, and improve, the natural history of genetic disorders. But such anticipatory management cannot occur unless the diagnosis is considered, either through screening programs or through identification and examination of an at-risk family members of affected individuals. Here too, specific diagnosis is a necessary component of proper patient identification, and hence, management.

Genetic Counseling

Genetic counseling has been defined as a communication process which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. In this process an appropriately trained person helps the individual or family comprehend the medical facts including the diagnosis, the probable cause of the disorder, and the available management. An appreciation for the way heredity contributes to the disorder, and the risk of recurrence in specific relatives is explained as well as options for dealing with the risk of recurrence. Discussions regarding options available to individuals in view of their risks and their family goals are another aspect of the genetic counseling process. Finally, the genetic professional helps the family make the best possible adjustment to the disorder in an affected member and/or to the risk of recurrence of that disorder.

Table 1
INHERITANCE PATTERNS OF GENETIC DISORDERS AND THEIR RECURRENCE RISKS

Inheritance Pattern	Example	Recurrence Risk	
		Sibling	**Offspring**
Autosomal Recessive	Cystic Fibrosis	25%	Near 0
Autosomal Dominant	Marfan syndrome		
Affected Parent		50%	50%
New Mutation		0	50%
X-Linked	Duchenne muscular dystrophy		
Carrier mother		Daughter-	Near 0
		Son-	50%
Multifactorial		3-5%	3-5%
Chromosomal			
Trisomy		<1%?	
Familial Translocation		<50%	<50%
De Novo Abnormality		0	Varies

Because each genetic disorder is relatively rare and because there are so many different genetic disorders each with unique manifestations and characteristic inheritance patterns, the fields of medical (clinical) genetics and genetic counseling have evolved. Since 1982, there have been certification examinations through the American Board of Medical Genetics for physicians in Clinical Genetics, Clinical Biochemical Genetics, Clinical Cytogenetics and Clinical Molecular Genetics and for Ph.D.'s in Medical Genetics, Clinical Biochemical Genetics, and Clinical Cytogenetics. In addition to subspecialty training in medical genetics, the physicians also have primary care medical expertise and usually Board Certification most commonly as pediatricians, internists, or obstetricians. The American Board of Medical Genetics has been recognized as an official member of the American Board of Medical Specialties by the American Medical Association. This designates Medical Genetics as an equal to the many other medical specialties in this country. Genetic counselors typically receive their training in two-year programs, resulting in a master's degree in genetics, and are certified by the American Board of Genetic Counseling. Genetic counselors are trained to communicate genetic risks, counsel patients and their families about the inheritance of genetic disorders and to help these families in the process of adjusting to these disorders.

Who Should Receive Genetic Counseling

The medical practitioner should consider referring patients or the close relatives of patients who have one or more of the following:

- A birth defect
- Abnormal mental development
- Abnormal physical growth or stature
- Abnormal sexual development or infertility
- Pregnant women 35 years of age and older
- Repeated pregnancy losses or miscarriages
- Pregnant women exposed to known or potential teratogens
- A known or suspected genetic disorder

- A chromosome abnormality
- A metabolic disorder
- Family history of cancer
- Consanguinity

Where to Obtain Genetic Diagnosis and Counseling

The following section summarizes the specific areas which come under the umbrella of "genetic services", and describe the ways to access such services in Arizona. Geneticists and genetic counselors consider it one of their primary roles to help patients and practitioners identify which patients could most benefit from genetic referral and where the closest genetic service providers are located.

There are three pediatric genetic programs in the state of Arizona:

The University of Arizona
Health Sciences Center
Department of Pediatrics
Section of Medical and Molecular Genetics
1501 North Campbell Avenue
P.O. Box 245073
Tucson, AZ 85724-5073
Phone: (520) 626-5175
Fax: (520) 626-8056

The University of Arizona
Phoenix Genetics Program
1300 North 12th Street, Suite 403
Phoenix, AZ 85006
Phone: (602) 239-4561
(800)752-7174
Fax: (602) 239-2207

Neonatology Associates, Ltd.
300 West Clarendon, Suite 375
Phoenix, AZ 85013
Phone: (602) 277-4161
Fax: (602) 274-3394

Genetic diagnosis and counseling are also available through programs at Children's Rehabilitative Services sites in Phoenix, Tucson, Yuma, Flagstaff, Sierra Vista, and outreach clinics at many of the Indian Health Service Clinics throughout the state. These programs are outlined in Section II.

In addition, there are four programs which provide prenatal diagnosis and genetic counseling, whose services are described in Section IV.

Arizona Institute for Genetics and Fetal Medicine
3200 North Dobson Road, Suite E-2
Chandler, AZ 85224
Phone: (480) 897-0234
Fax: (480) 897-0647

Phoenix Perinatal Associates
1331 North 7th Street, Suite 275
Phoenix, AZ 85006
Phone: (602) 258-7582
Fax: (602) 528-0099

Tucson Perinatal Services
5301 East Grant Road
P.O. Box 30280
Tucson, AZ 85712
Phone: (520) 795-8188
Fax: (520) 325-0809

University of Arizona
Health Sciences Center
Department of OB/GYN
Section of Maternal/Fetal Medicine
P.O. Box 245073
1501 North Campbell Avenue
Tucson, AZ 85724
Phone: (520) 626-6796
Fax: (520) 626-5115

SECTION II. CLINICAL GENETIC SERVICES FOR CHILDREN

Genetic Services In The Private Sector

The Department of Pediatrics, Section of Medical and Molecular Genetics of the University of Arizona offers clinical genetic services statewide. The genetics staff consists of medical geneticists, genetic counselors, a genetics nurse, and a metabolic nutritionist.

In Tucson, the genetics staff sees inpatient genetics consultations at Tucson Medical Center, University Medical Center, and St. Joseph's Hospital. To arrange inpatient consultations call the Section's office; or if after hours, contact the geneticist on call. Private outpatient services are arranged through the Section's Tucson office and patients are seen at the University Medical Center. Outside referrals are welcome. Patients in Yuma and Flagstaff can receive genetic services at their local Children's Rehabilitative Services (CRS) facility, even though they may not be CRS eligible. These appointments can be arranged by contacting the CRS facility.

The University of Arizona
Health Sciences Center
Department of Pediatrics
Section of Medical and Molecular Genetics
1501 North Campbell Avenue
P.O. Box 245073
Tucson, AZ 85724-5073
Phone: (520) 626-5175
Fax: (520) 626-8056

In Phoenix, the genetics staff sees inpatient consultations at Maricopa Medical Center, Phoenix Children's Hospital, St. Joseph's Hospital and Medical Center, Good

Samaritan Medical Center, Thunderbird Samaritan Medical Center, and Desert Samaritan Medical Center. To arrange inpatient consultations call the Section's office; or if after hours, contact the geneticist on call. Private outpatient services are arranged through the Section's Phoenix office and are seen at Phoenix Children's Hospital and St. Joseph's Hospital and Medical Center. Outside referrals are welcome.

The University of Arizona
Phoenix Genetics Program
1300 North 12th Street, Suite 403
Phoenix, AZ 85006
Phone: (602) 239-4561
(800) 752-7174
Fax: (602) 239-2207

Patients are also seen for private consultation by the following:

Neonatology Associates, Ltd.
300 West Clarendon, Suite 375
Phoenix, AZ 85013
Phone: (602) 277-4161
Fax: (602) 274-3394

Genetic Services Sponsored by State or Federal Agencies

Children's Rehabilitative Services (CRS)

The Children's Rehabilitative Services (CRS) is dedicated to providing quality, comprehensive, multi-disciplinary care to CRS-eligible members. CRS is in Arizona Department of Health Services' Office of Children with Special Health Care Needs (OCSHCN).

CRS is a statewide program available to children under 21 years of age residing in Arizona who meet medical and financial eligibility requirements. CRS accepts children with chronic illnesses or physically handicapping conditions which have potential for functional improvement. The program provides medical, surgical, rehabilitative, pharmacological, and allied health services as needed for members with eligible condition(s). **Routine pediatric care is not provided.** Services are provided through four regional contractors: St. Joseph's Hospital and Medical Center in Phoenix, and Children's Clinics for Rehabilitative Services in Tucson, Flagstaff, and Yuma. See Table 2 for specific site addresses and phone numbers. The program also provides traveling field clinics to outlying areas of the state.

Genetics Clinics

CRS provides clinical genetic services to established CRS members throughout the state. These services are provided by board certified medical geneticists and include full clinical evaluation, diagnosis, laboratory analysis, genetic counseling, treatment, and follow-up. Services from a board certified biochemical geneticist and a metabolic nutritionist are also available for CRS eligible children with metabolic disorders. All these services are provided in collaboration with the University of Arizona Health Sciences Center, Department of Pediatrics, Section of Medical and Molecular Genetics.

Genetics clinics are staffed by teams including a geneticist and genetic counselor or genetic nurse. These teams are made up of University of Arizona faculty based in Phoenix and Tucson.

Table 2

CRS CLINIC SITES

Flagstaff: Children's Health Center
1200 North Beaver Street
Flagstaff, AZ 86001
(520) 773-2054
(800) 232-1018

Phoenix: Children's Rehabilitative Services
124 West Thomas Road
Phoenix, AZ 85013
(602) 406-6400
(800) 392-2222

Tucson: Children's Clinics For
Rehabilitative Services
2600 North Wyatt Drive Tucson, AZ 85712
(520) 324-5437
(800) 231-8261

Yuma: Yuma Regional Medical Center
2400 Avenue A
Yuma, AZ 85364
(520) 344-7095

Central Arizona--Two full-day general genetics clinics are held every week for CRS members at St. Joseph's Children's Health Center in Phoenix. In addition, CRS regularly provides genetics services to CRS members in the following specialty clinics: meningomyelocele, metabolic, craniofacial, neurofibromatosis, and sickle cell.

Northern Arizona--Full-day genetics clinics are held six times a year for CRS members at the CRS clinic at Flagstaff Medical Center. In addition, metabolic clinics are provided twice yearly.

Southern Arizona--Two full-day genetics clinics are held every week at the Children's Clinics for Rehabilitative Services in the Tucson area. CRS, in addition to the general genetics clinic, also provides genetic services to eligible members in the following specialty clinics: neurocutaneous, meningomyelocele, metabolic, orofacial, cystic fibrosis, and sickle cell.

Western Arizona--Full-day genetics clinics are held six times a year for CRS members at the CRS clinic at the Yuma Regional Medical Center. In addition, metabolic clinics are held twice yearly.

Field/ Community Clinics--CRS also provides coordination for many Native American and rural community genetics services held at field/community clinics throughout Arizona.

Patients need to contact their local CRS facility to determine eligibility and to inquire about a genetics referral.

Indian Health Services

Clinical genetics services are provided to Native Americans statewide through a collaborative effort among the Indian Health Services, the University of Arizona, Department of Pediatrics, Section of Medical and Molecular Genetics, and Children's Rehabilitative Services. In addition to the field/community clinics provided through CRS, genetics clinics are also held in Parker, Fort Yuma, Sells, and Salt River. A genetics clinic is also provided to an urban Native American population at the Phoenix Indian Medical Center.

Referrals for genetic consultation can be arranged by calling the pediatric clinic at the individual clinic sites. See Table 3.

Table 3
INDIAN HEALTH SERVICES
FACILITIES OFFERING GENETICS SERVICES

Chinle (520) 674-7001
Fort Defiance (520) 729-5741 ext. 203
Fort Yuma (520) 572-0217
Kayenta (520) 697-3211
Keams Canyon (520) 738-2211
Phoenix Indian Medical Center (602) 263-1200
Parker (520) 669-2137
Peach Springs (520) 769-2204
Sacaton (520) 562-3321
Salt River (602) 379-4281
San Carlos (520) 475-2371
Sells (520) 383-7200
Tuba City (520) 283-2501
Whiteriver (520) 338-4911

CHILDREN'S INFORMATION CENTER (CIC)

The Children's Information Center is a statewide service for families, care givers, and health care professionals throughout Arizona provided by ADHS Office of Women's and Children's Health. The CIC bilingual toll-free number is 1-800-232-1676 or TDD (602) 256-7577.

The CIC is designed to help facilitate access to needed services for children with special needs by providing information, referrals, support, education and advocacy about services available to families in their own community and across the state.

Newborn Screening Program in Arizona

The Newborn Screening Program has been established in the Office of Women's and Children's Health at ADHS. The Program is responsible for administration of all newborn screening activities throughout the state. These activities include coordination with consulting specialists, physicians, and hospitals; follow-up of abnormal test results; education of health professionals and the general public; and monitoring of data associated with testing, billing for tests, and educational activities.

Testing of specimens is done by the Arizona State Laboratory through a contract with the Newborn Screening Program. Under Arizona State Law, babies born in Arizona routinely receive a first screen for the following disorders (with a recommendation for a second repeat screen):

- Phenylketonuria (PKU)
- Congenital Hypothyroidism
- Galactosemia
- Maple Syrup Urine Disease (MSUD)
- Homocystinuria
- Biotinidase Deficiency
- Hemoglobinopathies
- Congenital Adrenal Hyperplasia (CAH) may be added in year 2001

All but one of these disorders are autosomal recessive inherited disorders (only 5% of congenital hypothyroidism is inherited). Therefore, the same parents have a 25% recurrence risk with **each** subsequent pregnancy. The clinical consequences of these disorders may be prevented through early identification and intervention.

Timing of Specimen Collection

When a blood sample is collected, it is critical that all the information on the collection form be completed to allow for screening and rapid follow up of abnormal results. The blood specimen should be obtained at 72 hours of age or prior to discharge, which ever comes first. The first screen must be obtained before the baby leaves the hospital, as the chance of missing a baby with a disorder is much greater if the screen is never done than if done too early. A second screen is mandatory if the first screen was collected before the baby was 24 hours old and is recommended for all other babies. The second screen may soon be mandatory for all babies in Arizona.

Specimen Considerations

Invalid results may occur on:

- specimens collected prior to 24 hours after protein intake
- specimens collected prior to 36 hours of age
- specimens taken from infants after they have received a transfusion
- infants of low birth weight
- specimens taken from infants prior to 48 hours after they have received antibiotics
- infants on total parenteral nutrition (TPN) or soy formula

Submission of Specimens

All specimen collection cards are submitted to the Arizona State Laboratory for testing. The Arizona State Laboratory mails test results to all submitting physicians.

Arizona State Laboratory Services
1520 West Adams
Phoenix, AZ 85007
Phone: (602) 542-1187

Follow-up and Treatment

When a positive screening result is identified by the Arizona State Laboratory, the ADHS Newborn Screening Program is notified. The follow-up coordinators at the Newborn Screening Program notify the physician listed on the specimen collection card by telephone. If this is not the baby's primary care physician (PCP), the follow-up staff work to discover who

the PCP is, and inform the PCP of the results by telephone and subsequently by mail. The follow-up coordinators also notify the appropriate contracted physician specialist. The physician is advised to repeat a screen or perform confirmatory testing. The baby's PCP may also speak with one of Newborn Screening's physician consultants. The follow-up coordinators notify the parents of babies with a positive screening by mail which gives time for the PCP to contact the parents.

Follow-up coordinators can be reached by contacting:

Newborn Screening Program
Office of Women's and Children's Health
411 North 24th Street
Phoenix, AZ 85008
Phone: (602) 220-6465
Fax: (602) 220-6488

Metabolic Disorders

Diagnosis and treatment of **phenylketonuria**, **maple syrup urine disease**, **homocystinuria**, **galactosemia** and **biotinidase deficiency** are usually provided through a collaborative effort between the primary care practitioner (PCP) and a pediatric geneticist (see Table 5). Once the follow-up coordinators at the Newborn Screening Program notify the PCP and the consulting pediatric geneticist, the PCP advises the family to bring their infant in for confirmatory testing. If the test confirms a diagnosis for one of these metabolic disorders, the infant is eligible to receive medical services through Children's Rehabilitation Services (CRS) which is a statewide program with regional facilities (see the section on CRS for facility locations).

The serious consequences of these disorders may be prevented with prompt diagnosis and initiation of appropriate treatment. Following positive confirmation of **phenylketonuria**, **maple syrup urine disease**, **homocystinuria** or **galactosemia**, dietary treatment is begun immediately under the supervision of a geneticist and metabolic nutritionist. The infant is immediately switched to a special formula designed for each disorder. The infant's clinical status and the level of the specific blood metabolites levels are monitored. Dietary adjustments are made as needed, and nutritional counseling is scheduled. Continuation of the special diet is recommended **throughout life** for all four disorders to ensure the best possible outcome. This is especially important for females of reproductive age with PKU in order to reduce birth defects in their offspring.

Following confirmation of **biotinidase deficiency**, biotin is prescribed. Biotin supplementation is continued lifelong.

Endocrine Disorders

Follow-up diagnosis and treatment for **congenital hypothyroidism** and **congenital adrenal hyperplasia** are usually provided through a collaborative effort between the physician and a pediatric endocrinologist (see Table 5). Once follow-up coordinators at the Newborn Screening Program notify the PCP and the consulting pediatric endocrinologist of the positive screen, the PCP advises the family to bring the infant in for a confirmatory test. If the test confirms a diagnosis of **congenital hypothyroidism** or **congenital adrenal hyperplasia**, the child's treatment will be monitored by the physician with intermittent visits to a pediatric endocrinologist. Additionally, children with either of these endocrine disorders who meet the appropriate financial eligibility requirements may receive services through CRS (see the section on CRS for facility locations).

Following positive screening of **congenital hypothyroidism**, treatment is started immediately. Thyroid hormone (Synthroid) is prescribed on a daily basis. Endocrinology consultation or intermittent visits to a pediatric endocrinologist are important to assure proper management such as appropriate dosage of medication. Infants and children should undergo periodic developmental evaluations as these children are at risk for developmental and/or mental delays.

Congenital adrenal hyperplasia is a test that is likely to be added to the panel of newborn screens in the year 2000. With **congenital adrenal hyperplasia**, following confirmatory studies for diagnosis, treatment is started immediately. Glucocortico-steroids are prescribed on a daily basis. Endocrinology consultation or intermittent visits to a pediatric endocrinologist are important to assure proper management such as appropriate dosage of medication. Infants and children should undergo periodic developmental evaluations.

Hemoglobinopathies

Follow-up diagnosis and treatment for **hemoglobinopathies** are usually provided through a collaborative effort between the physician and a pediatric hematologist (see Table 5). Once follow-up coordinators at the Newborn Screening Program notify the PCP and the consulting pediatric hematologist of the positive screen, the PCP advises the family to bring the infant in for a confirmatory test. If the test confirms a diagnosis of **sickle cell disease** or **thalassemia,** the child's treatment will be monitored by the physician with intermittent visits to the pediatric hematologist.

The follow up coordinators refer the families of all babies with a positive **hemoglobinopathy** screen to the Arizona Chapter of the Sickle Cell Association of America for a thorough explanation of their child's screening results and genetic counseling to explain the implications of the child's hemoglobin findings. In addition, all positive screens for **sickle cell diseases** and sickle cell trait, hemoglobin C or D trait are referred to the ADHS Sickle Cell Anemia Program for long term follow-up. Children with **sickle cell disease** or **thalassemia** may receive medical services through CRS (see the section on CRS for facility locations).

For more information on the Newborn Screening Program or for a current listing of clinical providers/consultants, please call (602) 220-6465 and ask for the Newborn Screening Program.

SICKLE CELL ANEMIA PROGRAM (ASCAP)

The Arizona Sickle Cell Anemia Program, the result of a mandate by Arizona Public Health Law, is administered through the Office of Children with Special Health Care Needs (OCSHCN) in the Arizona Department of Health Services (ADHS). The Program provides long-term follow-up of sickle cell disease and trait, statewide education, free familial screening, and counseling services to "at-risk" populations as well as treatment services to affected children and adults through provider contracts with CRS.

Table 4
TREATMENT CENTERS FOR CHILDREN IDENTIFIED THROUGH THE NEWBORN SCREENING PROGRAM

Metabolic Disorders

The University of Arizona
Phoenix Genetics Program
1300 North 12th Street, Suite 403
Phoenix, AZ 85006
Phone: (602) 239-4561
Fax: (602) 239-2207

Metabolic Nutritionist
Phone: (800) 752-7174

The University of Arizona
Health Sciences Center
Department of Pediatrics
Section of Medical and Molecular Genetics
1501 North Campbell Avenue
P.O. Box 245073
Tucson, AZ 85724-5073
Phone: (520) 626-5175
Fax: (520) 626-8056

Congenital Hypothyroidism

Phoenix Children's Hospital
Pediatric Endocrinology
909 East Brill Street
Phoenix, AZ 85006
Phone: (602) 239-4844
Fax: (602) 253-0494

The University of Arizona
College of Medicine
Department of Pediatrics
Section of Pediatric Endocrinology
1501 North Campbell Avenue
Tucson, AZ 85724
Phone: (520) 626-6077
Fax: (520) 626-2881

Hemoglobinopathies

Pediatric Hematology/Oncology Assoc.
333 East Virginia Avenue, Suite 210
Phoenix, AZ 85004
Phone: (602) 253-5993
Fax: (602) 253-0466

University of Arizona
College of Medicine
Department of Pediatrics
Section of Hematology/Oncology
1501 North Campbell Avenue
Tucson, AZ 85724
Phone: (520) 626-6527
Fax: (520) 626-4137

Phoenix Children's Hospital
Sickle Cell Treatment Center
909 East Brill Street
Phoenix, AZ 85006
Phone: (602) 239-5785
Fax: (602) 239-3809

NUTRITION SERVICES FOR GENETIC DISORDERS

Nutrition services for infants and children with metabolic disorders were addressed in the previous section on **Newborn Screening.** Infants and children with other genetic diseases which are not screened for during the newborn period (such as organic acidurias, amino acidurias, cystic fibrosis, Prader-Willi syndrome, and failure-to-thrive), and children with other special health care needs may also be at risk for poor nutrition status. This may be due to feeding problems, drug/nutrient inter-actions, and altered growth patterns. Nutrition services and early intervention can have a positive impact on the health of this population and help to prevent further disabling conditions.

Nutrition services for these at-risk infants and children are available through Children's Rehabilitative Services at all four of the regional clinics in the state: Tucson, Phoenix, Yuma, and Flagstaff. See Table 2. Once a child is enrolled in CRS with an eligible medical condition, the child will receive nutrition services. If the dietitian is not a member of the team, a referral for services may be generated. The child will be assessed by a registered dietitian. A Nutritional Care Plan will be developed and followed.

Nutrition services are also available through the Department of Economic Security, Division of Developmental Disabilities (DDD) for developmentally disabled individuals who meet DDD eligibility requirements. Requests for nutrition services are coordinated through the six DDD district offices. See Table 5.

Table 5
DIVISION OF DEVELOPMENTAL DISABILITIES -DISTRICT CASE MANAGEMENT OFFICES

District I
1990 West Camelback Road, Suite 308
Phoenix, AZ 85015
Phone: (602) 246-0546

District II
P.O. Box 13178
Tucson, AZ 85732-3178
Phone: (520) 628-6800

District III
220 North Leroux
Flagstaff, AZ 86001
Phone: (520) 779-2731

District IV
350 West 16th Street
Yuma, AZ 85364
Phone: (520) 782-4343

District V
P.O. Box 1467
Coolidge, AZ 85228
Phone: (520) 723-4151

232 London Bridge Road
Lake Havasu, AZ 86403
Phone: (520) 453-7171

District VI
209 Bisbee Road
Bisbee, AZ 85602
Phone: (520) 432-5703

24 Hour Emergency
Phone: (602) 375-1403

Supplemental food, nutrition assessment, general education, and referral services are available for eligible infants and children less than 5 years old through WIC (Special Supplemental Nutrition Program for Women, Infants and Children) and the Commodity Supplemental Food Program (CSFP). Services are provided through local agency providers. Call 1-800-2525-WIC for further information on eligibility and clinic locations.

ARIZONA EARLY INTERVENTION PROGRAM

The Arizona Early Intervention Program (AzEIP) is a federally funded program administered through the Department of Economic Security. It provides services to any child between birth and 36 months of age who has not reached 50 percent of the developmental milestones expected at his or her age in the following domains:

- physical fine/or gross motor /sensory
- cognitive/adaptive
- language/communication
- social/emotional
- self-help/adaptive

Children from birth to 36 months with established conditions such as chromosomal anomalies, metabolic disorders, neural tube defects, significant auditory or visual impairment, or other diagnosed physical or mental conditions are likely to be eligible for these services. See Table 6.

Table 6
ARIZONA EARLY INTERVENTION PROGRAM SERVICES (AzEIP)
AREA OFFICES

DES AzEIP
3839 North 3rd Street, Suite 304
Phoenix, AZ 85012
Phone: (602) 532-9960
(888) 439-5609 toll free
Fax: (602) 200-9820

Call above number to obtain information on area offices.

BIRTH DEFECTS MONITORING

The Arizona Department of Health Services, Division of Disease Prevention began a program on January 1, 1987 which provides an important resource of information about a wide range of birth defects potentially causing death and disability in infants. This program, the Arizona Birth Defects Monitoring Program (ABDMP), was created as the result of an appropriation by the state legislature in 1986.

Approximately 78,000 births occur annually in Arizona. Based on an overall risk of 3-5% with each pregnancy, it is estimated that more than 2,000 children in Arizona are born yearly with reportable birth defects. Since there is variability in the recognition and reporting of both major and minor birth defects, the ABDMP collects only information on the major birth defects that are identified up to one year of age.

Goals and Uses of the Data

Approximately 500 conditions are monitored by the program including major malformations as well as chromosomal abnormalities. There are three goals of the program: first, to provide information on the incidence of specific birth defects, monitoring for "clusters" or unusual occurrences that might be associated with exposure to environmental factors (chemical, infectious agent, or other toxic substance); second, to provide a data base for continuing research into possible causes of birth defects so that strategies for prevention can be developed; and finally, to use the data for planning services that will assist the affected children and their families and allow for assessment of these programs.

The cause of most birth defects is not known. Inherited factors account for at least 10% of these defects. Another 5-10% of defects may be attributed to medication exposures, illicit drugs/chemicals, infectious agents, and environmental or occupational substances.

Data Input

Staffs of the ABDMP visit all hospitals which serve children in the state including Indian Health Services sites. Other sources, such as Children's Rehabilitative Services and centers providing genetic services, also contribute data on infants with birth defects. Through review of medical records at these facilities by the staff of ABDMP, information is abstracted on infants born on or after January 1, 1986 with specific birth defects.

Confidentiality

The information collected is entered into a confidential computer file at the Arizona Department of Health Services. Control procedures have been developed to make sure all information is kept strictly confidential and only statistical summaries will be released.

The Arizona Birth Defects Monitoring Program contributes to worldwide efforts while providing a valuable resource for the people of Arizona. For more information, please contact:

ARIZONA BIRTH DEFECTS
MONITORING PROGRAM
2700 North 3rd Street, Suite 4075
Phoenix, AZ 85004
(602) 542-7349

GENETIC SERVICES, OTHER

Umbilical Cord Blood Banking

Cord blood from a newborn baby can be stored for future use in treating serious cancers and immune system disorders. Cord blood has stem cells which contain vital components of the blood and immune system and has been used to treat more than 30 disorders. There is one center in Arizona which provides this service for a fee. More information can be found by calling 1-888-267-3256 or 1-888 CORD BLOOD.

SECTION III. CLINICAL GENETIC SERVICES FOR ADULTS (NON-PREGNANT)

Introduction and Overview

The vast majority of clinical genetic services in Arizona are directed toward the identification and treatment of genetic disease in children. This is partly because genetic conditions often become apparent early in life and/or are associated with medical or developmental problems. Unfortunately, many genetic conditions have no known treatment and death often occurs in infancy or childhood. Referrals for genetic services are common among those involved with the care of children in Arizona. Genetic services for adult populations, however, have been limited to at-risk pregnant women, while other adult populations have been under served. In addition, genetic service referrals may be dependent on health insurance approval rather than the actual presence of a genetic disorder. This is often the most restrictive step in the referral process, particularly in adult populations where referrals are made less frequently.

The impact of genetic disorders on adult populations is increasing for several reasons. Foremost is the advancing age of our society. It is expected that by the year 2030, 1 in 5 United States residents will be 65 years of age or older. A second factor is that many genetic disorders do not become apparent until adulthood or can be so variable that an individual may not know he or she is affected until later in life. Individuals may not even be aware that they have a genetic disorder in their family until a relative is diagnosed or an affected child is born. Medical research continues to identify genes and their phenotypic abnormalities for disorders not typically diagnosed until adulthood, such as Huntington disease. Third, results of research continue to support the presence of genetic influences in relatively common adult diseases such as heart disease, stroke, and cancer. As more is learned about the genetic basis of rare genetic disorders and the genetic influences of common chronic health problems, at-risk individuals may be identified earlier in life. This may reduce the numbers of individuals requiring long-term medical care for a chronic health problem. Referrals for genetic services in adult populations have been relatively few despite this increasing awareness within the medical community of the need for genetic services.

The arrival of new technologies has allowed researchers to begin to study the human genome (the entire human genetic makeup) in greater detail in an attempt to map the location and determine the function of all genes. New diagnostic gene tests and better carrier assessment through the identification of genetic mutations has and will dramatically increase the number of requests for adult genetic services. In addition, medical management of chronic genetic disorders has improved so that individuals with genetic disorders typically considered to be pediatric in nature are now surviving into adulthood. Physicians are also seeing other "pediatric" diseases in their adult patients. These include but are not limited to Turner syndrome, osteogenesis imperfecta (OI), phenylketonuria (PKU), cystic fibrosis, and other metabolic disorders.

As more information is learned about these types of genetic disorders, medical management issues are better defined. For instance, in past years children diagnosed with phenylketonuria were thought to require dietary control of phenylalanine for only the first several years of life. It is now realized that dietary control of phenylalanine should be lifelong to avoid a gradual loss of IQ and decrease the likelihood of hyperactivity and attention deficit disorder. In addition, it is now well recognized that women with PKU must maintain excellent dietary control of their phenylalanine prior to conceiving and maintain this control throughout pregnancy or risk teratogenic (birth defect causing) effects of elevated phenylalanine. Pregnancies of women with PKU who have been "off diet" are at a significant risk for spontaneous loss, intrauterine growth retardation, microcephaly, congenital heart disease, and mental retardation.

Chromosome analysis has been a com-mon screening test to use in the evaluation of children with multiple malformations and/or developmental delay/mental retardation. Adults may also benefit from chromosome analysis in selected circumstances.

Reproductive failure has commonly been the reason for performing chromosome analysis on adults. Couples with 3 or more miscarriages have an increased risk for being carriers of balanced chromosomal translocation that predispose them to having offspring with unbalanced chromosomal rearrangements. This could result in miscarriage or the birth of a child with multiple congenital anomalies.

Adults who experience infertility should also have chromosome analysis performed, if no other explanation has been determined. For instance, Klinefelter syndrome (47,XXY) is associated with infertility in an otherwise healthy male. Subtle features of Klinefelter syndrome may be overlooked but may include tall stature, small testes, mild breast development, and a

female-like distribution of body hair. Women with primary or secondary amenorrhea (early menopause) are also at an increased risk to have a chromosome abnormality,
specifically of the X chromosome. Therefore, these studies should be considered in the evaluation of such women. Usually women with abnormalities of one of the X chromosomes will have short stature and may resemble a patient with Turner syndrome. However, secondary sexual characteristics may be present, particularly in women with premature menopause. Adults with Klinefelter syndrome, Turner syndrome and other variations of the X chromosome may benefit from an endocrine evaluation. Many males with the diagnosis of Klinefelter syndrome benefit from testosterone replacement therapy. Women with Turner syndrome or other more subtle abnormalities of their X chromosome may develop osteoporosis without estrogen replacement therapy.

Carrier Testing

Carrier testing for many genetic disorders is presently available. It is usually offered to those families who already have a diagnosis of a genetic disease in a close relative or to those of specific ethnic backgrounds. Each individual carries approximately 5-10 hidden recessive genes that do not function properly. Although they do not cause problems in the carrier state (a single copy), offspring are at risk for genetic disorders if a partner also carries the same recessive gene. Since ethnic background influences the likelihood of being a carrier for certain disorders, it is appropriate to offer targeted population screening. Such screening is presently available for sickle cell disease in the African American population, Tay-Sachs disease in the Ashkenazi Jewish and French Canadian populations, thalassemia in Mediterranean and Asian populations and cystic fibrosis in the Caucasian population. Cystic fibrosis carrier testing is more accurate, however, in those families where a child with cystic fibrosis has had a positive identification of the mutation(s) responsible for his/her disease. Families with a positive history of other genetic disorders may also have gene testing available to them, although this is disease specific. Anyone with a documented family history of a genetic disorder should contact their local genetics facility to see if testing is available.

Presymptomatic Testing

Some genetic disorders do not present until later adulthood, despite the fact that an individual carries the defective gene throughout life. If the gene has been identified, testing may be available to determine if an individual carries the gene prior to manifesting the condition. This is called presymptomatic testing. Diseases which have presymptomatic testing presently available include, but are not limited to, adult polycystic kidney disease, Huntington disease, and certain types of cancer.

Because there is no current treatment for Huntington disease and other similar disorders, programs have been established that ensure individuals have had the proper education, medical evaluation, and counseling prior to undergoing testing. Before obtaining blood samples for Huntington disease, breast cancer gene testing, and other predictive testing, contact should be made with the local clinical genetics provider(s) to determine specific details of these testing programs.

CANCER GENETICS (ADULT/PEDIATRIC)

General Introduction

One area of genetics that is rapidly expanding is the field of cancer genetics. Genes responsible for specific cancers are being sought and mapped to chromosomal locations. Not only may we gain a greater understanding of the role that genetics plays in the development of cancer, but the clinical application of this technology cannot be underestimated.

Generally, cancer is seen as a collection of diseases of multifactorial etiology. In other words, there are combinations of predisposing environmental and hereditary factors which interact to produce malignancies. These factors can be classified along genetic and environmental gradients. Examples of strictly environmental inducers include known carcinogens and radiation exposure. Lifestyle choices such as diet, smoking, delayed childbearing, and occupation may be contributing factors in some individuals. In some cases, heredity plays a major role. In these families, a single gene predisposes the majority of individuals who inherit this gene to develop cancer.

Inherited factors can contribute to the occurrence of cancer in various ways. It is widely recognized that cancer is caused

by acquired genetic alterations within specific cells of the body (somatic mutations); thus all cancer could be considered genetic, although not specifically inherited from a parent. It is estimated that overall, about 10-20% of all cancer cases have a familial nature (several affected family members). This estimate varies by cancer with almost 40% of retinoblastoma due to inheritance of a single mutated gene, whereas only 5-10% of breast cancer has a strong hereditary influence.

Classification

Expression of inherited factors can be seen in 1) hereditary cancer susceptibility syndromes, 2) hereditary pre-neoplastic syndromes, 3) chromosomal aneuploidy, and 4) multifactorial familial clusters.

Hereditary Cancer Susceptibility Syndromes

Hereditary cancer susceptibility syndromes are rare, single gene disorders in which the cancer initiation is caused by a germline mutation (inherited) in a specific gene. These are characterized by autosomal dominant inheritance of a mutated gene with a high degree of penetrance, i.e., most people who inherit the mutation develop cancer. In these syndromes, malignancy is the central feature.

A number of pediatric and adult cancers of this type are known. These include basal cell nevus, dysplastic nevus, breast-ovarian cancer, familial adenomatous polyposis (FAP also includes Gardner, Oldfield, Turcot, and Zanca syndromes), hereditary nonpolyposis colon cancer (HNPCC, Lynch syndrome types I & II), Li-Fraumeni syndrome, multiple endocrine neoplasia (MEN) types I & II, retinoblastoma (RB), site-specific breast cancer, site-specific ovarian cancer, von Hippel-Lindau, and Wilms tumor (WT).

Hereditary Pre-Neoplastic Syndromes

Hereditary pre-neoplastic syndromes are those associated with cancer as an occasional finding rather than a primary feature of the syndrome. There are over 100 syndromes that fall into these categories and they are sub-classified into five groups:

- Chromosomal instability disorders, such as ataxia telangiectasia (AT) and Bloom syndrome
- Genodermatoses which affect the skin and other organs, e.g., albinism and neurofibromatosis (NF)
- Immunodeficiency syndromes, e.g., Chediak-Higashi and Wiskott- Aldrich
- Overgrowth disorders, e.g., Beckwith-Wiedemann and hemihypertrophy
- Phacomatoses, e.g. Cowden familial adenomatous polyposis (FAP), and von Hippel-Lindau syndrome.

A given syndrome may belong to several of these groups. These syndromes have different Mendelian inheritance patterns including autosomal dominant, recessive, and X-linked inheritance.

Neurofibromatosis type I (NF-I) is a common autosomal dominant disorder with classical features of multiple café-au-lait spots, macrocephaly, learning disabilities, scoliosis, and benign neurofibromas. Individuals with this diagnosis are at risk for malignancies, such as neurofibrosarcoma and pheochromocytoma.

Persons with basal cell nevus syndrome can have jawbone cysts, dysmorphic features, and multiple pigmented nevi which have a high likelihood of transformation to basal cell carcinomas in adulthood. Generally, the malignancies arise due to increased incidence of mutations or inability to repair those mutations which naturally occur.

Cancer Due to Aneuploidy

Individuals diagnosed with various chromosomal abnormalities may have increased risks for cancer. These include trisomies 13, 18, and 21; Klinefelter syndrome (47,XXY); and Turner syndrome (45,X). Malignancies sometimes seen in the trisomies are teratomas, leukemias, Wilms tumor, hepatoblastomas, and neurogenic tumors. Males with Klinefelter syndrome have a significantly increased lifetime risk for developing breast cancer that approaches the baseline risk for women. They also are at risk for extra-gonadal germ cell and testicular tumors. Individuals with Turner syndrome may develop gonadal tumors, post-estrogen endometrial tumors, or leukemia. Those with mosaicism involving Y chromosome material are especially vulnerable.

Familial Cancers

Cancers of the breast, ovary, colon, endometrium, lymphoid and hemopoietic tissue, and brain often seem to cluster in families due to collections of polygenic, multifactorial, and single-gene causes which are only now being discovered. First-degree relatives of cancer patients within families recognized to contain familial clustering generally have a relative risk of approximately 2-3 times over the general population risk.

Breast cancer is the most common cancer among Western women. It may occur sporadically as a small familial cluster of one to two cases or be due to strong hereditary predispositions. Approximately 60-70% of cases are sporadic, 10-20% familial, and 5-10% hereditary. The incidence of breast cancer varies with age, geography, family history, and a variety of risk factors involving interactions of genetic, hormonal, and environmental factors. The general risk for first-degree relatives of affected individuals is increased 2-3 fold. These risks can be further quantified per decade of life using published tables of empirical risk figures that depend on various combinations, such as age of onset, bilaterality, number of generations affected, and other factors. More refined risk estimates will become available as various susceptibility genes are identified. Identification of hereditary breast cancer genes (e.g. Li-Fraumeni syndrome, breast-ovarian, site specific) are important for accurate counseling, medical surveillance, and susceptibility testing.

Ovarian cancer is rarer than breast cancer, but poor prognosis due to late diagnosis in a large proportion of cases significantly contributes to its high mortality. The lifetime risk for women to develop ovarian cancer is less than 1%. Risk for women with one affected first degree relative is about 5%. While most ovarian cancer is not hereditary, it is important to recognize the 5-10% due to inherited syndromes such as site specific ovarian, breast-ovarian, and heredity non-polyposis colon cancer (HNPCC). Another contributing factor is reproductive history, showing increased risk with infertility, and decreased risk with use of birth control pills.

Colon cancer is one of the most common cancers among both men and women in Western countries. Like breast cancer, familial clusters may be due to combinations of multiple factors such as genetics, diet, alcohol, colitis, obesity, and predisposing polyps. First degree relatives of familial cases have a 3-fold increased risk for developing colon cancer. Hereditary cases are generally divided into hereditary polyposis syndromes such as familial adenomatous polyposis (FAP) and Puetz-Jegher syndrome and hereditary non-polyposis syndromes, Lynch syndromes and Muir-Torre.

CANCER GENES

The types of genes involved in the development of cancer are ones which generally involve the regulation of cell growth and differentiation. When changes in these genes are inherited, these are called cancer susceptibility genes. Three types of cancer genes will be discussed: oncogenes, tumor suppressor genes and mutator genes.

Oncogenes

Oncogenes are activated forms of normal cellular genes called protooncogenes. Activation can occur through viral insertion, point mutation, chromosomal rearrange-ment, or gene amplification. When activation occurs, the cell loses control of pathways that control growth and differen-tiation. Oncogene changes are often seen in malignant tissue. However, only one oncogene is known to be inherited, the *ret* gene, associated with multiple endocrine neoplasia, type II. MENII includes cancers of several endocrine tissues, such as pituitary, parathyroid, pancreatic islet cells, thyroid, adrenal cortex, and pheochromocytoma.

Tumor Suppressor Genes

Whereas oncogenes lead to accelerated growth, tumor suppressor genes maintain normal growth. A person may lose function of one copy of a tumor suppressor gene through mutation, deletion, chromosomal rearrangement, or mitotic nondisjunction. One mutated copy may be inherited as an autosomal dominant trait. However, both tumor suppressor genes need to be mutated to result in uncontrolled cell growth which may result in the formation of a tumor. Therefore, if an individual inherits an alteration in one copy of a tumor suppressor gene, he/she is vulnerable to malignant transformation through a second loss in a tumor suppressor gene in targeted organs. Persons with inherited mutations in tumor suppressor genes tend to manifest an increased number of cancers, at earlier ages than usual, in bilateral organs, or even formation of primary tumors in several different organs.

Common tumor suppressor genes are:

- APC associated with FAP
- DDC associated with colon cancer
- p53 associated with many types of tumors
- RB altered in retinoblastoma
- WT1 mutations associated with Wilms tumor
- BRCA1/BRCA2 associated with breast and/or ovarian cancer

Mutator Genes

Mutator genes, also known as DNA mismatch repair genes, are a new class of genes discovered in 1993. Mutations in mutator genes cause cells to progressively accumulate replication errors. If these errors occur in genes important in controlling cell growth and differentiation, then malignancy could result.

Two genes implicated in the risk for hereditary non-polyposis colon cancer (HPNCC) are involved in detecting and correcting errors in matching the nucleotide pairs during DNA replication (analogous to the spell checker function on a computer). These have been called MLH-1 on chromo- some 3 and MSH-2 on chromosome 2.

Mutations of one copy of a mismatch repair gene can be inherited in an autosomal dominant pattern. However, expression (as in the tumor suppressor gene) requires inactivation of both copies. It is when a change occurs in the second gene that the replication errors begin to accumulate resulting in a tumor that is positive on a particular molecular analysis of the tumor.

CANCER SUSCEPTIBILITY TESTING

Genetic studies have the potential to improve the accuracy of cancer risk estimates. However, the testing also carries the potential for serious emotional, social, and economic problems. Therefore, it is critical that genetic susceptibility testing for cancer should occur only on a voluntary basis in persons with an indication of increased genetic risk and psychological readiness. Adequate pre-and post-test counseling and thorough informed consent should occur in the context of a comprehensive cancer risk counseling session.

Genetic susceptibility testing begins with affected relatives from families that have a documented, high incidence of cancer. The relatives with cancer are tested first, and if they have a specific cancer gene mutation, then testing of unaffected relatives is performed.

The availability of cancer susceptibility testing will be limited until a number of research questions are addressed. In the interim, families can be referred for comprehensive cancer risk counseling and possible DNA banking of tissue of affected relatives for future testing.

CANCER RISK COUNSELING

Cancer risk counseling is a communication process concerning an individual's possible increased risk of developing specific forms of cancer. This type of counseling includes obtaining detailed family, medical, and lifestyle histories; documentation of cancer-related diagnoses; pedigree construction and analysis; risk assessment and counseling; and discussion of options for early detection and prevention. The risk counselor must deal with the individual's risk for developing specific malignancies; the chances of carrying cancer susceptibility genes; the person's perception of risk; and occasionally, cancer risks for offspring.

Discussion of cancer risk frequently includes explanations of the multi-step process of cancer development, patterns of inheritance, and how risk estimates are derived. The individual is thus provided with a framework for understanding risk estimates and can make more informed and thoughtful decisions. Psychological ramifications and the possible need for further support services must also be considered.

The process of cancer risk counseling generally involves more and longer sessions than is customary in other types of genetic counseling appointments. Cancer counseling is generally offered by a masters level, nationally certified genetic counselor, an advanced practice oncology nurse, or other health professional with equivalent or greater training. Minimally, the cancer risk counseling service should involve both genetics and oncology information, and optimally, be done by a multidisciplinary team which should also include a mental health professional, health educator, surgeon, dietician, social worker, and epidemiologist. Factors useful in identifying individuals at an increased risk for cancer are listed in Table 7.

Table 7
CLUES TO IDENTIFYING INDIVIDUALS AT INCREASED GENETIC RISK OF CANCER

1 Cancer in both paired organs (e.g., both breasts).

2 More than one focus of cancer in a single organ (e.g., multiple retinoblastomas in one eye).

3 Two or more distinct cancers (e.g., breast and ovarian).

4 Cancer that occurs at an unusual age (e.g., breast cancer under 40 years).

5 Cancer that occurs in an unusual site (e.g., osteosarcoma in the mid-humerus).

6 Cancer that occurs in the less commonly affected sex (e.g., breast cancer in males).

7 Cancers occuring in association with other conditions [e.g., multiple café-au-lait spots neurofibromatosis); multiple colon polyps (familial adenomatous polyposis)].

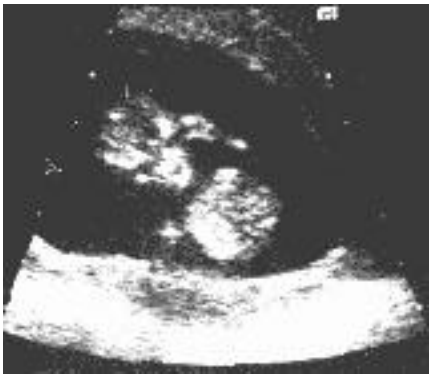
8 Unusual or rare tumors (e.g., pheochromocytoma).

9 First degree relative with one of the above or two first degree relatives with cancer.

SECTION IV. CLINICAL GENETIC SERVICES FOR PREGNANT WOMEN AND COUPLES OF REPRODUCTIVE AGE

Prior To Pregnancy

While most pregnancies result in the birth of a normal baby, couples may be able to optimize their pregnancy outcome by awareness of family and personal health issues.



The woman and her partner should be aware of their family histories. Some birth defects/conditions can be inherited or occur in several family members. A family history of a prior child or close relative with a chromosome abnormality, congenital defect, mental retardation, or genetic condition should prompt a referral for a preconceptual genetic consultation.

The woman and her partner should be aware of their ethnic backgrounds since certain genetic disorders are more common in some ethnic groups. For example, individuals from Eastern European Jewish or French Canadian populations are at increased risk for Tay-Sachs disease, while sickle cell anemia is more frequent in those of African ancestry. Individuals of Mediterranean or Asian descent more commonly manifest a genetic anemia known as thalassemia.

Women with certain chronic illnesses or disorders should seek evaluation with a high-risk pregnancy specialist prior to conception. These disorders include:

- Diabetes (insulin dependent)
- High blood pressure
- Maternal PKU (phenylketonuria)
- Seizure disorders
- Genetic conditions such as Marfan syndrome, Ehlers-Danlos, myotonic dystrophy, achondroplasia

When considering pregnancy, certain agents may increase the risk for birth defects or fetal complications and should be avoided. These include:

- Accutane
- Alcoholic beverages
- Anticonvulsant medication
- Jacuzzis/hot tubs
- Radiation exposure
- Recreational drugs
- Occupational chemical exposure
- Thalidomide
- Tobacco usage

Recent medical studies indicate preconceptual intake of folic acid (one of the B vitamins) decreases the risk for spina bifida by 60%. It may also reduce the occurrence of other birth defects such as heart defects, genitourinary abnormalities, and clefts. Since most pregnancies are not planned and the vitamin must be taken prior to and throughout pregnancy, it is recommended that all women of childbearing age supplement their diet with 0.4 mg of folic acid daily (100% of RDA). Folic acid is contained in most multi-vitamins, but is also present in some foods such as dark, green leafy vegetables, broccoli, liver, fortified cereals, and orange juice. For women who have had a previous pregnancy or child with a neural tube defect, 4 mg. of folic acid daily is recommended. This amount of folic acid is not recommended on a long-term basis, and should only be taken in the one to three months prior to conception and the first trimester of pregnancy.

Prenatal Genetic Counseling

Prenatal genetic counseling is the process by which a trained genetic counselor obtains, evaluates, and reviews a couple's family and medical history. Their risks for abnormalities are discussed as are many diagnostic or screening procedures which may offer them reassurance that their pregnancy is proceeding normally.

Review of the Family and Medical History

The first step in prenatal genetic counseling is to obtain and review the couple's medical and family history. Detailed information regarding the occurrence of any birth defect(s), mental retardation, or genetic disease is obtained along with information about the family's ethnic background and general health. If risks are identified, their genetic basis, if any, is discussed with the family.

Review of the Diagnostic Procedures

Prenatal genetic counseling also involves the discussion of which diagnostic or screening procedures and laboratory tests may help the family to evaluate the pregnancy. A review of the benefits, limitations, and risks of any procedure or laboratory test helps the family to be informed about their options. They then will know the appropriate time during pregnancy for testing to be scheduled, how the testing and procedures are performed, and when the results will be available.

Informed Consent

Prenatal genetic counseling allows the family to understand the risks and to make an informed decision as to what, if any, testing is appropriate for them and their pregnancy. This is particularly important with invasive diagnostic procedures such as amniocentesis, chorionic villus sampling, or fetal blood sampling. Although small, there are risks associated with these procedures.

Results and Follow-up

Since the majority of women under-going prenatal testing have risks for fetal abnormalities which are less than 1-2%, most results are normal. In these cases, follow-up with the family is usually done by telephone. If the results are abnormal, the family may be seen for follow-up counseling to review the diagnosis, its implications, and available options. With such cases, prenatal genetic counseling plays an important role, not only in relaying to the family information necessary for them to make decisions regarding the pregnancy, but also in providing emotional support for the family.

Who Should Have Prenatal Genetic Counseling

Any couple who has concerns that they may be at risk for having offspring with birth defects, mental retardation, or genetic disorders should consider prenatal genetic counseling. Although most prenatal genetic counseling is performed after conception has occurred, it is best if couples seek counseling preconceptually.

The most common indications for referral are:

- Maternal age 35 or greater at time of delivery
- Abnormal maternal serum AFP/ multiple marker screening results
- Chromosome abnormality or rearrangement in the couple or their family
- Previous pregnancy with a chromosome abnormality

- Couples with three or more miscarriages

- Carriers for genetic disorders such as Tay-Sachs disease, sickle cell disease cystic fibrosis, hemophilia, or muscular dystrophy

- Affected with a genetic disorder such as achondroplasia, phenylketonuria (PKU), cystic fibrosis, or sickle cell anemia

- Family history of spina bifida or anencephaly

- Family history of a previous child or parent with a physical defect that may be diagnosed by ultrasound such as cleft lip, heart, or kidney defects

Who Provides Prenatal Genetic Counseling

Prenatal genetic counseling is most often performed by specially trained genetic counselors under the supervision of a medical geneticist. Genetic counselors usually have a masters degree in human genetics and genetic counseling and certification is granted through the American Board of Genetic Counseling.

In some cases, particularly in rural areas where access to genetic services may be limited, prenatal genetic counseling is sometimes provided by physicians who also perform amniocentesis and other diagnostic services. In these situations, close interaction with a prenatal genetics program is encouraged.

Prenatal Diagnostic and Screening Procedures

Until recently, the only technique available for prenatal diagnosis was **second trimester amniocentesis.** Although it remains the most widely used procedure for genetic prenatal diagnosis, several other new and effective techniques are now clinically available and being used in Arizona. These include **chorionic villus sampling (CVS), early amniocentesis, high resolution ultrasound, percutaneous umbilical blood sampling (PUBS),** and, to a lesser extent, **fetal skin biopsy**. It is recommended that genetic counseling be a prerequisite to any of these procedures and that the experience of the practitioner performing such testing be ascertained in order to minimize any procedural risks or complications.

In addition, the past several years have seen the development of screening tests such as **maternal serum alpha-fetoprotein (MS-AFP)** and **multiple marker screening** as well as **primary ultrasound** which may help with the identification of pregnancies at increased risk for specific fetal abnormalities.

Amniocentesis

Second trimester amniocentesis is usually performed at 15 to 16 weeks gestational age. Recently, amniocentesis performed between 12.0-14.9 weeks gestational age has become available as a diagnostic procedure. This test is referred to as **early amniocentesis** and technically is done in the same manner as mid-trimester amniocentesis. Both procedures are performed by transabdominal placement of a needle under ultrasound guidance into the amniotic sac. A sample of amniotic fluid is withdrawn and sent for chromosome analysis, as well as amniotic fluid alpha-fetoprotein (AF-AFP) to help rule out a fetal neural tube defect.

The most common use for either second trimester or early amniocentesis is to diagnose fetal chromosome abnormalities. Trisomy 21 (Down syndrome) is the most frequent abnormality detected. However, amniotic fluid and its cells can also be used to diagnose a large number of genetic disorders when the need is indicated by prior family history. Such testing usually involves specialized techniques which analyze biochemical or DNA markers in the amniotic fluid. The total number of genetic disorders that can be diagnosed by all these techniques is increasing exponentially, and consultation at a genetic center is indicated when any patient has a history or risk factor for a possible genetic disorder.

The miscarriage rate of mid-trimester amniocentesis is between 1/200 and 1/400 depending upon the center and the experience of its practitioner. While early amniocentesis has the benefit of providing results somewhat sooner in a pregnancy, the procedure-related risk is higher than that for mid-trimester amniocentesis. The risk of miscarriage related to early amniocentesis may range between 1/100 to 1/130. While small, the risk of other complications following either amniocentesis procedure include cramping, bleeding, infection, chronic amniotic fluid leakage, or premature labor.

Chorionic Villus Sampling (CVS)

Chorionic villus sampling has recently been proven and accepted to be a safe and effective alternative to amniocentesis. It is generally performed between 10-12 weeks of gestational age, by either a transcervical or transabdominal route. Individual clinical circumstances may favor one approach over another.

The obvious advantage to this procedure is a diagnosis made earlier in pregnancy than that obtained with either the early or mid-trimester amniocentesis procedure. However, CVS has risk factors higher than that of amniocentesis, with the miscarriage rate ranging between 1/50 to 1/100 (1-2%), depending upon the experience of the practitioner. Other possible complications are similar to those listed for the amniocentesis procedures. There has recently been a concern about the possible association of CVS and birth defects. A few studies have shown an increased risk of limb defects in cases with CVS performed before 9 weeks of gestation. In most centers in Arizona, CVS is not performed earlier than 10 weeks of gestation. Published data from the Centers for Disease Control and Prevention in Atlanta, Georgia, suggest the risk for limb abnormalities associated with CVS may be approximately 1 in 3000.

CVS is most often used to diagnose fetal chromosome abnormalities; although like amniocentesis, many different genetic disorders can also be diagnosed when medically indicated. However, CVS does not permit screening for neural tube defects, and therefore, women who undergo CVS should follow-up with a MS-AFP screening test after 15-16 weeks gestational age.

High-Resolution Fetal Ultrasound

High-resolution, targeted or complete ultrasound (also referred to as **Level II ultrasound**) has become an important and non-invasive diagnostic tool for the detection of many structural malformations associated with genetic disorders. Such technology is best performed using state-of-the-art high resolution equipment with the experience of a specialist who has knowledge of genetics and the causes of malformations. As such, it is primarily performed at referral genetics centers. Frequent indications for the use of high resolution ultrasonography include:

- Suspected congenital malformation of the spine, brain, heart, abdominal wall, genitouinary, or gastrointestinal system
- Fetal evaluation secondary to abnormal laboratory results such a MS-AFP/multiple marker screening
- Fetal evaluation secondary to maternal conditions such as insulin-dependant diabetes
- Fetal evaluation secondary to suspicious findings on preceding ultrasound exam.

The list of reliably diagnosable disorders is extensive and growing rapidly. Whenever there is a family history of any abnormality or a prenatally suspected malformation, consultation with one of the prenatal diagnostic centers in Arizona should be obtained.

Umbilical Blood Sampling

Fetal umbilical blood sampling, also called percutaneous umbilical blood sampling (PUBS), is available at prenatal diagnostic centers in Arizona. It is performed u s AFP/matalt referrtief genetiary toly suspected mal65sampling79ructural TD -185.

Where Is Prenatal Genetic Counseling and Testing Available in Arizona

The following programs offer services in the area of prenatal genetics including prenatal genetic counseling and diagnostic procedures:

Arizona Institute for Genetics and
Fetal Medicine
3200 North Dobson Road, Suite E-2
Chandler, AZ 85224
Phone: (480) 897-0234
Fax: (480) 897-0647

Tucson Perinatal Service
5301 East Grant Road
P.O. Box 30280
Tucson, AZ 85712
Phone: (520) 795-8188
Fax: (520) 325-0809

Phoenix Perinatal Associates
1331 North 7th Street, Suite 275
Phoenix, AZ 85006
Phone: (602) 257-8118
Fax: (602) 528-0099

University of Arizona
Health Sciences Center
Department of Obstetrics and Gynecology
Section of Maternal/Fetal Medicine
1501 North Campbell Avenue
P.O. Box 245078
Tucson, AZ 85724
Phone: (520) 626-6796
Fax: (520) 626-5115

Prenatal Screening Tests

As noted earlier, there are several prenatal screening tests which have recently been developed or have become more widely used as ultrasound equipment is now frequently found in obstetricians offices. These tests include **MS-AFP** or **multiple marker screening** and **primary obstetrical ultrasound.** These evaluations are most often performed by a woman's obstetrician, but abnormal screening test results or suspicious ultrasound findings, should prompt a referral to a prenatal diagnostic center for genetic counseling and additional fetal evaluation.

Maternal Serum Alpha-Fetoprotein Screening

Alpha-fetoprotein (AFP) is a glycol-protein produced by the fetus throughout pregnancy and is present in amniotic fluid and maternal serum. When the fetus has certain types of defects, the amount of AFP in the amniotic fluid and maternal serum is often elevated. Maternal serum alpha-fetoprotein (MS-AFP) was first developed as a screening test in the 1980's to determine if a woman was at increased risk for carrying a fetus with an open neural tube defect (anencephaly or myelomeningocele). After this test had been used for several years, some studies showed that the MS-AFP level may be low if the fetus had a chromosome abnormality, particularly Down syndrome (Trisomy 21). This finding led to the expansion of MS-AFP screening inter-pretations to calculate a risk for having a fetus with Down syndrome. When combined with maternal age, this screening can identify 15-20% of pregnancies at risk for Down Syndrome in women less than 35 years of age.

However, because 75% of infants with Down syndrome are born to mothers under 35, and MS-AFP screening has limited sensitivity, an alternative screening method has been developed. A combination of proteins, which may include **MS-AFP** as

well as **unconjugated estriol(uE3)** and **human chorionic gonadotropin (hCG),** and inhibin. This test, known as **multiple marker screening,** is available to screen for Down syndrome and in some cases Trisomy 18, another chromosome abnormality. The use of multiple markers increases the sensitivity of Down syndrome screening above that of MS-AFP alone.

When properly used, MS-AFP screening is extremely valuable in the early detection of serious birth defects. It must be remembered, however, that the purpose of any **screening test** is to estimate the chance that an abnormality may be present; **it does not make the diagnosis**. Screening programs are designed to miss as few as possible affected fetuses (false negatives), while keeping the number of women with unaffected fetuses, but an abnormal test result to a minimum (false positives). With this understanding by both the physician and patient, anxiety will be minimized and MS-AFP screening becomes an effective tool in the identification of pregnancies at risk for certain disorders.

Factors Affecting MS-AFP Interpretation

MS-AFP screening is optimally performed between 16 and 18 weeks gestation for neural tube defect screening and 15 to 19 weeks gestation for Down syndrome screening.

Since abnormal levels of MS-AFP and other fetal proteins may be predictive of adverse pregnancy outcome, it is important that results be correctly interpreted. Since many non-fetal factors can affect the level of these proteins, it is important that the laboratory performing the test take into account maternal age, weight, race, multiple gestation, and maternal insulin-dependent diabetic status. Gestational age, preferably based on ultrasound measurements, is critical for accurate screening results. Most laboratories performing MS-AFP testing will report the results as a **multiple of the median (MOM)** value and each may have their own normal cut-off ranges. You should contact the laboratory to be assured that it makes all the appropriate adjustments when interpreting the test. Unadjusted values increase the likelihood of false negative and false positive results.

Elevated MS-AFP

When MS-AFP is measured singly or as a part of the multiple marker screen, it can sometimes be elevated above the MOM normal range. An elevated MS-AFP value can be reflective of open neural tube defects, abdominal wall or open skin defects, renal defects, fetal teratomas, or other congenital malformations. It may also be due to incorrect gestational dating, multiple pregnancy, fetal demise, placental abnormalities, or it may be a non-specific finding. If the patient's gestational age has not been confirmed by ultrasound, obtaining this information is useful before proceeding with further evaluation. If the patient's gestational age is correct, the patient should receive genetic counseling to review the implications of the elevated MS-AFP and discuss options for additional testing. This may include high resolution ultrasound to look for structural malformations and possibly amniocentesis for testing of the amniotic fluid AFP and acetylcholinesterase (AChE). AChE is an enzyme produced in the nervous system, and when found, strongly suggests an open neural tube defect is present. The absence of AChE suggests that the AFP elevation is from a source other than an open neural tube defect.

With elevated AFP and normal results on ultrasound an/or amniocentesis, the pregnancy may be considered "high risk" due to the increased incidence of stillbirths, intrauterine growth retardation, maternal toxemia, placental abruption, or premature labor in women with otherwise unexplained MS-AFP elevations. Such pregnancies should be closely monitored throughout the remainder of gestation.

Low MS-AFP or Abnormal Multiple Marker Screening

With a low adjusted MS-AFP value, there is an increased likelihood of overestimation of gestational age, fetal death, molar pregnancy, missed abortion, or fetal chromosome abnormality. The most common chromosome abnormality, identified through MS-AFP screening, is Down syndrome.

Using multiple marker screening, a pattern of the protein levels plus maternal age gives a determination of the fetal Down syndrome risk and in some cases, Trisomy 18. In general, MS-AFP and unconjugated estriol levels tend to be low, while human chorionic gonadotropin levels are elevated. A concern for Trisomy 18 is raised when all protein values are low. If the risks from either MS-AFP single test screening or multiple marker screening are equal to or greater than the risk of a 35 year old woman to have a fetus with Down syndrome in the second trimester, then **genetic counseling and amniocentesis for fetal chromosome analysis** should be offered. Low MS-AFP or abnormal multiple marker screening tests **should not be repeated**

Patient Selection and Education

The MS-AFP screening tests have increasingly become a part of routine prenatal care. A 1985 alert from the Professional Liability Committee of the American College of Obstetricians and Gynecologists (ACOG) stated that it is "imperative that every prenatal patient be advised of the availability of this test and the patient's decision with respect to the test be documented in the patient's chart."

A 1994 release from the Clinical Practice Committee of the American College of Medical Genetics recommends serum screening should be offered to all women less than 35 years of age unless a positive family history suggests CVS or amniocentesis is indicated. There is controversy regarding the use of multiple marker screening in patients aged 35 and older. If all women age 35 and older underwent amniocentesis, 100% of Down syndrome pregnancies in this group would be detected. If only multiple marker screening was used as an indicator, 10-15% of Down syndrome cases would be missed in the 35 and older age group. An additional concern is that multiple marker screening may not identify other fetal aneuploidies which mostly occur in older mothers and outnumber Down syndrome pregnancies in this population. The current recommendation of this group and a 1994 ACOG Committee on Obstetric Practice Opinion is that serum screening **should not** replace amniocentesis or CVS testing in women aged 35 years or older.

With the complexity and variety of prenatal screening and diagnostic testing, patient education regarding options should ideally be reviewed with a genetic counselor. Pamphlets and other written information are useful, but do not replace discussion with a genetic counselor. The patient needs to have a clear understanding that **maternal serum alpha-fetoprotein and multiple marker screening are not diagnostic tests**. A normal test result does not guarantee a normal pregnancy outcome nor does an abnormal result always indicate an abnormal fetal outcome. Raised patient anxiety is frequently the result of inadequate patient education.

Where to Obtain MS-AFP Screening

There are many laboratories that perform MS-AFP and/or multiple marker testing both within Arizona and in other states. A number of issues are important in selecting a laboratory to perform MS-AFP/multiple marker screening. Does the laboratory report results as MOM values? Does it have its own reference data for normal ranges per gestational week? Does it adjust for the factors known to affect MS-AFP/multiple marker values including gestational age, weight, race, and insulin-dependent diabetes? Does it adjust its normal ranges for maternal age when screening for Down syndrome? Does it participate in an external quality control program? Does it have epidemiologic monitoring, i.e., keep a record of the number of patients whose MS-AFP values fall outside the high or low cut-off points?

Please also consult the section on **Choosing a Reference Laboratory for Genetic Services in Section V.** for additional qualifications.

Primary Obstetrical Ultrasound

Primary obstetrical ultrasound, sometimes known as a **Level 1 ultra-sound scan**, is generally performed for pregnancy dating or size/date discrepancy or to identify multiple gestations or fetal demise. It is possible that a primary scan may identify an abnormality or finding for which the health care provider desires further detailed evaluation, thus prompting a referral for a **high resolution or targeted obstetrical ultrasound**. It is imperative that both primary and targeted obstetrical ultra-sounds conform to the Guidelines for Obstetrical Sonography.

New Techniques for Prenatal Diagnosis

There are several new techniques currently undergoing investigational study which may in the future offer either very early genetic diagnosis or a method which would allow more generalized fetal testing. These two methods are preimplantation genetic testing and testing of fetal cells in maternal serum. At the present time, neither of these procedures are available at genetic centers in Arizona.

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis is the term used to describe the application of molecular genetic techniques to diag-nose genetic disorders in embryos prior to implantation in the uterus. Although not yet an established or widely available procedure, it has been designed to offer couples at high risk for having offspring with genetic disorders an alternative to more traditional methods of prenatal diagnosis such as CVS or amniocentesis.

This procedure combines the techniques of in vitro fertilization (IVF), embryo biopsy and genetic testing. After an egg cell is fertilized by a sperm in a laboratory (i.e., IVF), the cell reproduces itself many times forming an embryo. A few of these cells can be removed from the embryo (embryo biopsy) so that the genetic information in the cells can be analyzed using specialized tests. Following this testing, unaffected embryos can be transferred to the uterus to establish pregnancy. By performing this type of testing, parents can avoid passing on a genetic disorder without having to make difficult decisions regarding pregnancy termination.

This testing option is very labor intensive and thus very expensive. It is also likely that only a small percentage of pregnancies will occur following embryo transfer to the uterus. Preimplantation genetic diagnosis does not insure the birth of a healthy child, but it can greatly decrease the likelihood of passing on a specific genetic disorder in some families. Unfortunately, this procedure is not currently available in Arizona, and interested couples must be referred to centers out of state.

Fetal Cells in Maternal Blood- Noninvasive Prenatal Diagnosis

Fetal nucleated cells in the maternal circulation constitute a potential source of cells for noninvasive prenatal diagnosis of fetal abnormalities. Several cell types are being investigated for their usefulness in prenatal diagnosis.

The Arizona Teratogen Information Program

Definition and Description

A teratogen is any substance which harms an unborn baby, leading to structural or functional disability or spontaneous loss of pregnancy. It has been estimated that 5-10% of birth defects are due to an exposure during pregnancy to a drug, chemical, infectious, or physical agent. Exposures during pregnancy are common and may increase anxiety in pregnant women. One study found that pregnant women in the United States were exposed to an average of seven medications, chemicals, or other agents.

Potential teratogens may take several forms: prescription medications, over-the-counter drugs, environmental chemicals, therapeutic radiation, and maternal infections. While the number of well-documented human teratogens is small, prevention of exposure in these situations may be possible. Thalidomide is a classic example of a human teratogen. It was initially marketed in the early 1960's and was shown to cause limb, heart, hearing, and developmental abnormalities in exposed children. Thalidomide has been re-released in the United States for use in the treatment of the HIV wasting syndrome. However, thalidomide is also being considered for use in individuals with autoimmune disorders of which a disproportionate number are women of reproductive age. A rigid protocol for prescribing and distributing thalidomide has been instituted to limit the number of exposures during pregnancy. Currently, some prescribed medications which are documented to have teratogenic effects include those used to control seizures, blood clotting, hypertension, and acne. Recreational drugs such as alcohol, tobacco, and cocaine have been recognized to have an impact on the developing fetus. Exposure to certain industrial chemicals and waste products have been linked to decreased fertility in men and increased rates of miscarriage in women. Radiation in therapeutic doses can be associated with growth and mental retardation. Finally, certain maternal infections increase the risk of birth defects, including rubella, cytomegalovirus, herpes virus, toxoplasmosis, and parvovirus (Fifth disease).

Factors in Teratogen Counseling

When counseling for teratogens, close attention must be paid to the specific agent, dosage, timing of exposure, and a maternal medical history. The timing of exposure is crucial with the most sensitive time for malformations thought to be during organogenesis in the first trimester. However, growth and development particularly of the brain occur throughout pregnancy. The use of multiple substances can have additive effects, leading to a more significant adverse outcome. The medical condition of the mother may also be important. This often leads to a discussion of the risks and benefits of a particular exposure. Scientific data concerning out-comes of exposed pregnancies is often conflicting, difficult to locate, and hard to interpret. Much of the data are in the form of case reports, animal studies, and occasional retrospective reviews. In addition, species specific sensitivities exist whereby agents that cause birth defects in animals may have little or no effect in humans. In order to provide complete information, it may be necessary to consult various resources. It is important to understand the relevancy of available information regarding a particular agent in order to provide a risk assessment on which pregnancy management may be based.

The Arizona Teratogen Information Program (ATIP)

The Arizona Teratogen Information Program is funded by the Arizona state legislature. It consists of three parts: a toll free phone service, education, and research. It is a joint effort of the University of Arizona's Department of OB/GYN, Section of Maternal/Fetal Medicine, the Department of Pediatrics, Section of Medical and Molecular Genetics, and the Arizona Poison and Drug Information Center. Calls during daytime hours will be answered by one of several teratogen information specialists (TIS). After hours, Poison Information Specialists will answer emergent calls or take messages for the TIS to follow up on the next working day. The TIS staff will obtain a thorough history including exposure, family medical information, and pregnancy and personal medical history. A risk assessment is made after review of the appropriate literature and the information is relayed to the client by phone. If a significant risk to the baby is identified, a formal consultation is strongly recommended with either a genetic counselor or geneticist. Methods of fetal evaluation appropriate to the situation will be discussed.

This program is offered free of charge to any person in the state of Arizona. To obtain information concerning reproductive effects of an exposure, call:

Arizona Teratogen Information Program Pregnancy Riskline
1-888-285-3410 or
(520) 626-3410

SECTION V. CYTOGENETIC AND MOLECULAR LABORATORY TESTING

Cytogenetics

The analysis of human chromosomes has been used as a part of clinical diagnosis for nearly 30 years. During this time, and particularly in the past decade, the technology has improved significantly. The number of clinical conditions for which chromosome analysis is helpful continues to increase rapidly. Depending upon the specific diagnosis, chromosome analysis can now be performed on a variety of tissues. The indication, tissue type, and cytogenetic techniques used can vary from case to case. This section reviews the indications for chromosome studies, the range of techniques available, and will provide information about cytogenetic laboratories within Arizona.

Human cells normally have 46 chromosomes arranged into 23 pairs. The sex chromosomes, XX (female) or XY (male), comprise one of these 23 pairs. Chromosomes are packages of genes, the units of hereditary information containing the genetic code. Visible abnormalities include changes in the number or structure of the chromosomes. Although a large number of genes may be involved in these abnormalities, it is not possible to see alterations of a single gene or a small group of genes with classical standard cytogenetic techniques. These gene abnormalities must be studied with biochemical or molecular genetic tests. In general, any extra or missing genetic material is associated with birth defects, growth retardation and/or developmental delay/mental retardation. It is the task of a cytogenetic laboratory to guide the physician in the choice of the appropriate tissue type and test requested and to identify and characterize these chromosome abnormalities.

Who Should Have Chromosome Analysis

In the best of all worlds, every individual would know about his or her chromosomes. However, population karyotyping (chromosome analysis) is not realistic at this time. On the other hand, there are many people for whom chromosome analysis is indicated, but the studies are deferred until the situation becomes urgent. Many times they are simply not done, and therefore, diagnoses are missed. The following is a list of circumstances in which the likelihood of a chromosome abnormality is substantial. In these cases, it would be appropriate for the clinician to request chromosome studies to confirm the diagnosis or to assist in the management of the patient.

Indications for Chromosome Studies

Obstetrics/Prenatal/Reproductive

- Infertility
- Multiple (three or more) spontaneous miscarriages
- Previous child with a chromosome abnormality, other than a trisomy
- Chromosome rearrangement in the family
- Stillbirth
- Advanced maternal age (35 or older at delivery)
- Abnormal maternal serum screening (MS-AFP, multiple marker screen)
- Maternal anxiety

Pediatric and Adult

- Multiple congenital malformations
- Ambiguous genitalia
- Developmental delay or mental retardation
- Abnormal pubertal development
- X-linked recessive disease in females (hemophilia, Duchenne muscular dystrophy, etc)
- Chromosome instability syndromes (ataxia telangiectasia, Bloom syndrome, dysplastic nevus syndrome, Fanconi anemia, etc.)

Leukemia and Cancer

- Possible or proven leukemia
- Possible or proven lymphoma
- Benign or malignant solid tumor
- Bone marrow transplantation

When there is any doubt about the indication or the appropriate sample needed for performing chromosome studies, the physician should contact the cytogenetic laboratory **before** obtaining the specimen.

How To Obtain A Sample For Chromosome Analysis

Cytogenetic analysis involves culturing living cells, capturing them during the cell cycle in which the chromosomes are appropriately condensed and visible, differentially staining them by one of several techniques, and examining them for alterations in number or structure. Exam-ination is done first under the microscope. Then the chromosomes are either photographed, or captured digitally, and arranged in a standardized paired pattern (a karyotype) so that members of each chromosome pair can be examined together. A variety of tissues can be used to study human chromosomes. It is important to select a tissue which is appropriate for the clinical indication under consideration.

Blood is most often used because it is easily obtained, relatively quick to grow, and easy to study. The analysis of blood chromosomes requires a minimum of 30 hours.

Bone marrow may also be used for chromosome analysis in the neonate and in cases of leukemia. Since cells in bone marrow are rapidly dividing, they can be analyzed within hours. In the case of leukemia, cells from the bone marrow should be analyzed over two or three cell cycles in order to find chromosome abnormalities associated with the disease.

Skin can be used as an alternate source of cells. This is especially appropriate when there is a concern about mosaicism, which is the presence of two or more cell lines with different chromosome constitutions within one individual. When a macerated stillbirth or abortus prevents using skin or blood, other tissues can also be used such as cells from an internal organ, connective tissue, or placenta.

Prenatal cytogenetic diagnosis requires **amniotic fluid** cells, **chorionic villus sampling (CVS)** or a **percutaneous umbilical blood sample (PUBS). See Section IV.** for additional information regarding these procedures.

Care must be taken to maximize the viability of the cells. Chromosome studies can only be obtained from **living cells**. This means that conditions of transportation to the laboratory are critical, especially temperature. All samples being transported the same day should be kept at room temperature. Other than **amniotic fluid,** all samples should be refrigerated if not shipped until the next day. Blood and bone marrow should not be allowed to clot. **Sodium heparin is the anticoagulant of choice**. Blood or bone marrow can also be drawn into a sterile syringe containing liquid sodium heparin. Tissues should never be placed in formalin because it **kills** the cells. Sterile isotonic solutions, preferably cell or blood culture media, should be used for tissue samples. All samples, especially amniotic fluid and CVS samples, should be collected and maintained under sterile conditions. Any variable which compromises cell viability may jeopardize the chromosome study.

Techniques Of Analysis

Numerical changes such as the extra chromosome 21 associated with Down syndrome are easily detected. Structural chromosome changes such as large translocations, deletions, or duplications also may be detected with a **standard/ routine** chromosome study. However, in some disorders, there are subtle changes which involve a minute portion of the chromosome (microdeletions). These may only be detected with **high resolution chromosomes** which have been specially treated to lengthen the chromosomes. There are also molecular tests which may be used when high resolution chromosome analysis is normal, but the clinical diagnosis still suggests a microdeletion syndrome (See FISH, found later in this section). To ensure the most accurate diagnosis, the physician can help the laboratory by providing as much clinical information as possible.

Choosing a Reference Laboratory for Genetic Studies

The physician should select a high quality, licensed cytogenetics laboratory which can provide accurate results with an appropriate turn-around-time.

In this day of diverse and complex health care systems, it is even more important for the physician to be able to rely upon the laboratory to perform ordered tests with accuracy, reproducibility, and appropriate interpretation. Since genetic testing is used less frequently than many other types of testing, it is essential to know the capabilities of the laboratory. The physician who orders the test is the person ultimately responsible for the accuracy of the results and of course, the steps taken as a consequence of those results.

For these reasons, the following guidelines are recommended by the National Committee on Clinical Laboratory Standards for choosing and evaluating a reference laboratory for genetic studies. It is advisable for you to review the following standards.

Personnel Education And Experience

- Is the laboratory director board certified by the American Board of Medical Genetics in Clinical Cytogenetics?
- Do other laboratory personnel have licensure and certification?
- Do personnel participate in continuing education?

Quality Assurance

- Does the lab participate in inter-laboratory proficiency testing programs?
- Does the lab document and review proficiency test results?
- Does the lab participate in voluntary accreditation programs, certification, and/or licensure?
- Does the lab comply with CLIA '88 and make their Quality Assurance Plan available?

Efficiency

- Does the lab maintain instructions on special needs for specimen collection, preservation, and transportation?
- Does the turn-around time for specific samples fit the following guidelines?
  - Amniotic fluid- 7-14 days
  - CVS- 7-14 days
  - Routine bloods- 7-14 days
  - STAT bloods- 30-48 hours
  - High Resolution bloods- 14-21 days
  - Bone marrows- 2-7 days
  - Tissues- 10-21 days
- Does the lab report abnormal results by phone or FAX?
- Will the lab provide consultation if necessary?

The state of Arizona maintains an Office of Laboratory Licensure and Certification whose purpose is to see that a high standard of quality is maintained among state licensed laboratories. If you have questions about a laboratory, please call (602) 542-6100.

Where to Obtain Cytogentic Studies

Chromosome studies can be performed at the following Arizona laboratories:

Palo Verde/Sonora Quest Lab
1255 West Washington
Tempe, AZ 85281
Phone: (480) 685-5700
(800) 365-4363
Fax: (480) 685-5750

IMPATH*
810 East Hammond Lane
Phoenix, AZ 85034-6515
Phone: (602) 254-6620
Fax: (602) 254-7340
*cancer cytogenetics only.

St. Joseph's Medical Center
DNA Diagnostics Laboratories
350 West Thomas Road
Phoenix, AZ 85013
Phone: (602) 406-3585
Fax: (602) 406-4118

University Medical Center
Department of Pathology
Cytogenetics Laboratory
1501 North Campbell Avenue
Tucson, AZ 85724
Phone: (520) 694-7107
Fax: (520) 694-2077

In some cases, insurance companies are contracted with specific laboratories. These may include the above listed laboratories or ones out-of-state. Prior to sending samples, contact the laboratory to determine the status of contracted insurance plans.

Fluorescent in Situ Hybridization (Fish)

Fluorescent in situ hybridization (FISH) analysis permits the DNA of the chromosomes to be observed microscopically. DNA fluorescent probes are constructed to attach to specific genes or to coat (paint) the entire chromosome. The signals emitted by these probes can be detected with a fluorescence microscope. The number of signals detected corresponds to the number of genes or targeted chromosomes that are present.

Normal human cells would have two copies of each autosomal gene or whole chromosome. The presence of only one signal would indicate a loss of the targeted genetic material. The presence of more than two signals would indicate extra targeted genetic material. These types of studies provide more specific information about a small portion of a chromosome not visible previously by routine chromosome analysis.

Indications For FISH Analysis

- High resolution banding studies are normal but the diagnosis is consistent with a specific microdeletion syndrome such as Prader-Willi, Angelman, Cri-du-Chat, Wolf-Hirschorn, Miller-Dieker, and Di George/Velocardiofacial syndromes. (New microdeletion probes are being introduced continually.)

- One chromosome is known to be abnormal, but the area of concern is too small to identify.

! To help identify the chromosome origin of marker chromosomes.

! Clinically important changes in specific genes such as the t(9;22 rearrangement that characterizes chronic myeloid leukemia.

Molecular Testing

Molecular DNA techniques now allow us to examine the specific genes which are responsible for certain human diseases. These techniques can be used for presymptomatic diagnosis, prenatal diagnosis, and carrier testing of genetic disease. The number of DNA tests which are available continually increases. If there is a question regarding the availability of DNA testing for a specific disease, contact one of the genetic service providers listed on pages 8 and 9.

Table 8
SOME CONDITIONS FOR WHICH DNA TESTING IS CURRENTLY AVAILABLE

Huntington disease
Duchenne muscular dystrophy (DMD)
Myotonic dystrophy
Hemophilia
Sickle cell disease
Thalassemias
Alpha-one antitrypsin deficiency
Cystic fibrosis
Fragile X syndrome
Achondroplasia
Spinal muscular atrophies (childhood)
Breast cancer
Neurofibromatosis
Adult-type polycystic kidney disease

The above diseases are only a sampling of those for which DNA testing is available.

How is DNA Testing Performed

There are two approaches to performing DNA testing for genetic diagnosis. For many conditions such as cystic fibrosis and the hemoglobinopathies, we are able to use **direct methods** to look at the gene by identifying the mutation(s) responsible for the condition. There are often several, different mutations that can result in the same disorder. For instance, over 200 separate mutations have been identified for cystic fibrosis.

Laboratories

St. Joseph's Hospital & Medical Center DNA Diagnostics Laboratories
350 West Thomas Road
Phoenix, AZ 85013
Phone: (602) 406-3585
Fax: (602) 406-4118

How and Where to Send Specimens for DNA Testing

DNA can be extracted from any cell which contains a nucleus. Most commonly this is performed by using white cells from a peripheral blood sample or from a fibroblast culture grown from a skin biopsy or amniotic fluid. Identification of the appropriate laboratory, specimen requirements, and costs for testing the patient can be made by contacting your local genetics facilities listed elsewhere in this booklet. Each laboratory which performs DNA testing has a written protocol which should be obtained under optimum circumstances. Since molecular laboratories have not come under CLIA '88 regulations, care must be used in selecting a laboratory. Insurance companies may influence the laboratory to which a sample may be sent.

Who Is A Candidate For DNA Testing

Individuals who have a family history of a genetic disorder for which molecular genetic analysis is available are appropriate candidates for this type of testing. If a genetic disorder is known or suspected in a family, it is important to check on the availability of DNA-based testing **prior** to obtaining the specimen.

Genetic counseling is a vital component of molecular genetic testing. Patients need to understand their risks for the disorder, the accuracy of the testing process, the fact that such testing often involves multiple family members, the frequent psychological consequences of learning of a high risk for a genetic disorder, and the confidentiality of the process. In most cases, the patient will benefit more by direct referral to a clinical genetics center for genetic counseling and coordination of the testing process. Close communication with the referring physician and the genetic counselor or geneticist will keep everyone fully informed.

Sample *DNA Analysis Patient Information and Consent* form at the back of this booklet.

SECTION VI. SOURCES OF INFORMATION FOR PEOPLE AFFECTED BY GENETIC DISEASE OR BIRTH DEFECTS

Arizona Resources

Arizona Center for Disability Law
3839 North 3rd Street, #209
Phoenix, AZ 85012
Phone: (602) 274-6287
(800) 927-2260
Fax: (602) 274-6779

Arizona Center for Disability Law
3131 North Country Club, #100
Tucson, AZ 85716
Phone: (520) 327-9547
(800) 922-1447
Fax: (520) 323-0642

Children's Information Center
(800) 232-1676

Children's Rehabilitative Services
1740 West Adams, #200
Phoenix, AZ 85007
Phone: (602) 542-1860
Fax: (602) 542-2589

Clinics: Phoenix: (602) 406-6400
(800) 392-2222
Tucson: (520) 324-5437
(800) 231-8261
Flagstaff: (520) 773-2054
(800) 232-1018
Yuma: (520) 334-7095

Emily Anderson Family Learning Center
909 East Brill Street
Phoenix, AZ 85006
Phone: (602) 239-6902
Fax: (602) 239-4670
E-mail: emilyc@phxchildrens.com
Website: www.phxchildren.com/programs/emilycenter

March of Dimes Birth Defects Foundation
1616 East Indian School Road, #200
Phoenix, AZ 85016
Phone: (602) 266-9933
(888) 566-9933
Fax: (602) 266-9793
Website: www.modimes.org

March of Dimes Birth Defects Foundation
7290 East Broadway, #G-2
Tucson, AZ 85710
Phone: (520) 298-5490
Fax: (520) 298-5584

Pilot Parents of Southern Arizona
2600 North Wyatt Drive
Tucson, AZ 85712
Phone: (520) 324-3150
(877) 365-7220
Fax: (520) 324-3152
e-mail: ppsa@pilotparent.org

RAISING Special Kids
4750 North Black Canyon, #101
Phoenix, AZ 85017
Phone: (602) 242-4366
(800) 237-3007
Fax: (602) 242-4306

Regional & National Resources

Alliance of Genetic Support Groups
4301 Connecticut Avenue NW, #404
Washington, DC 20008-2304
Phone: (202) 966-5557
(800) 336-GENE
Fax: (202) 966-8553
E-mail: info@geneticalliance.org
Website: http:// www.geneticalliance.org

Mountain States Genetics Network
Colorado Dept. of Public Health
4300 Cherry Creek Drive South
Denver, CO 80246-1530
Phone: (303) 692-2423
Fax: (303) 782-5576
Website: http://www.ahsc.arizona.edu/msrgsn

National Human Genome Research Institute, National Institutes of Health
9000 Rockville Pike, 49/3A14
Bethesda, MD 20892-6050
Phone: (301) 496-0844
Fax: (301) 402-0837
Website: http://www.nhgri.nih.gov

National Organization for Rare Disorders (NORD)
P.O. Box 8923
New Fairfield, CT 06812-8923
Phone: (203) 746-6518
(800) 999-NORD (6673)
Fax: (203) 746-6481
E-mail: orphan@rarediseases.org
Website: http://www.rarediseases.org

Office of Rare Diseases
National Institute of Health
31 Center Drive, MSC 2082
Room 1B03
Bethesda, MD 20892-2082
Phone: (301) 402-4336
Fax: (301) 402-0420
E-mail: sg18b@mh.gov
Website: http://www.rarediseases.info.nih.gov/ord/

The Arizona Genetics Advisory Committee is working on a fax broadcast which will be sent periodically via fax regarding selected genetics topics. If you would like to receive these short, up to date faxes, please call: in Phoenix, U of A, Phoenix Genetics Program at (602) 239-4561 or fax (602) 230-2207; or in Tucson, U of A, Section of Medical and Molecular Genetics at (520) 626-5175 or fax (520) 626-8056.